June 28, 2004

Via Fax and UPS

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket Nos. 2004D-0187, 2004D-0188, 2004D-189
Draft Guidances for Industry on Premarketing Risk Assessment; Development and Use of Risk Minimization Action Plans; and Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment; Availability; 69 FR 25130 (May 5, 2004)

Dear Sir/Madam:

Aventis Inc. and Aventis Pasteur together (collectively referred hereinafter as "Aventis") are pleased to provide the following comments on the above-referenced draft guidances for industry entitled "Premarketing Risk Assessment", "Development and Use of Risk Minimization Action Plans", and "Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment". These draft guidances provide guidance to industry on risk management activities for drug products, including biological drug products, in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). The draft guidances address, respectively, premarket risk assessment; the development, implementation, and evaluation of risk minimization action plans for drug products; and good pharmacovigilance practices and pharmacoepidemiologic assessment of observational data.

General Comments

We applaud the Agency's efforts in putting together the latest guidance documents on risk management. We are particularly pleased that the draft guidances now reflect that for most products, appropriate product labeling along with good post-marketing surveillance should be the risk management program for the majority of drugs. Any assessment and decision about a risk management plan should be based on the benefits as well as the demonstrated risk profile of a drug product. Further, risk assessment must continue throughout the life cycle of the product.

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Requirements for additional safety data should be grounded in evidence and genuine medical/scientific concerns.

While we agree and support most of the concepts addressed in these guidance documents, we strongly recommend that FDA adopt internationally accepted definitions and that the terms be used consistently throughout the documents. We also suggest that FDA add a glossary for all the definitions in the guidances.

We also recommend that FDA provide when applicable, flow charts for further clarification.

The following are our suggestions for the Agency's consideration to further refine each guidance:

Guidance I- Premarketing Risk Assessment- Docket No. 2004D-0187

General Comments

We suggest that definitions be given in a Glossary. We also notice that some definitions are lacking (e.g. signal) and recommend the use of ICH standard terminology.

We are concerned that increasing the size of the population in clinical trials and the battery of tests to identify as many risks as possible prior to approval will slow down the approval process and will complicate the safety and efficacy assessment. The significant increase in the cost of drug development would not necessarily deliver an increase in understanding of product safety.

Specific Comments

II. B. Overview of the Risk Management Guidances

Lines 65-66: *"...many of the recommendations presented here focus on situations when a product may pose* ***an unusual type or level of risk.***"

Aventis recommends that FDA be more specific on the definition of "an unusual type or level of risk". We suggest that the Agency clarify that the guidance applies only to those established risks, and not to hypothetical risks having no clinical relevance. For instance, specific risks of concern for a drug should drive any risk reduction activities, not theoretical risks with no clinical relevance. Decision on risk management plans must be based on scientific evidence. (Same comment applies to guidances on Risk MAP, lines 76-77, and guidance on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, lines 77-79)

III. THE ROLE OF RISK ASSESSMENT IN RISK MANAGEMENT

Line112-113: "*...this guidance focuses on risk assessment during the later stages of clinical development, particularly during phase 3 studies.*"

Aventis suggests that the title of this guidance make it clear that this guidance focuses on later stage risk development.

IV.A Size of the Premarketing Safety Database

Lines 146-147: "*Some risks become apparent only when a product is used in tens of thousands or even millions of patients in the general population.*"

Aventis agrees that even if we increase the number of patients in clinical trials (which is limited because of feasibility), we may not see some risks and may not be able to avoid them.

Line 160-162: "*A larger safety database may be appropriate if a product's preclinical assessment or human clinical pharmacology studies identify signals of risk that warrant additional clinical data to properly define the risk.*"

Aventis recommends that FDA specify what a "larger safety database" means. Is it larger than 1500 patients, as mentioned in line 192 referring to EA1 guidance? Aventis also asks for clarification on how large a database should be for preventive vaccine (see Line 224)

Lines 167-168: "*Sponsors are therefore encouraged to discuss with the relevant review division the appropriate size of the safety database for such products.*"

Aventis agrees that all products are not the same, and the need for and types of risk management activities should be considered on a product-by-product basis.

IV. B. Considerations for Developing a Premarketing Safety Database

Lines 240-243: "*Because data from multiple trials are often examined when assessing safety, it is particularly critical to examine terminology, assessment methods, and use of standard terms to be sure that information is not obscured or distorted.*"

We agree with the needs for standardization and ask the FDA to continue to accept MedDRA as the dictionary for standard terminology.

Lines 285-288: "*Inclusion of a diverse population allows for the development of safety data in a broader population that includes patients previously excluded from clinical trials, such as the elderly (particularly the very old), patients with concomitant diseases, and patients taking usual concomitant medications.*"

Aventis agrees with the need to broaden inclusion/ exclusion criteria to find an adequate study patient population and to reflect an accurate picture of usage in the real world. However, it will

also require increased sample size, and the assessment of both efficacy and safety will be more difficult because of the increased number of potential confounding factors.

IV. C. Detecting Unanticipated Interactions as Part of a Safety Assessment

Aventis believes that examination for unanticipated interactions requires the following:

1- an in-depth knowledge of the mechanism of action of the product. This is difficult not only for a new drug, but also for older drugs (e.g. for aspirin) as well as for vaccines (knowledge will increase with immunology development)
2- knowledge of all potential concomitant drugs or vaccines that may be taken,
3- complete information about subjects

This would be ideal to achieve, however, it is not feasible in pre-marketing stage.

Lines 356-357: "*One important way to detect unexpected relationships is by incorporating pharmacokinetic (PK) assessments (e.g., population PK studies) into a subset of clinical trials, including safety trials.*"

We suggest that FDA provide clarification on what pharmacokinetic assessments mean for vaccines.

V.A. Risk Assessment During Product Development

Lines 429-432: "*If a product is to be studied in pediatric patients, special safety issues should be considered (e.g., effects on growth and neurocognitive development if the drug is to be given to very young children/infants; safety of excipients for the very young; universal immunization recommendations and school entry requirements for immunization).*"

Aventis agrees that there should be special attention on populations that will receive the product and it is justified to conduct studies in appropriate subjects. Nevertheless, the tests to be performed systematically in these populations should be standardized. This is very important for vaccines given to million of children (e.g. Autistic Spectrum Disorders should be tested with appropriate tests)

Lines 460-463: "*When there are early signals (i.e., preclinical or clinical) of serious toxicities or other unique or special considerations (e.g., regarding the safety of the use of the product with a concomitant medication where the previous clinical data have not addressed the issue sufficiently). In such cases, LSSS data could help better characterize the risk.*"

Aventis recommends that FDA provide a definition for "signal". Is FDA referring to the WHO definition?

Line 466-469: "*The use of a large trial may increase the chance of showing the product to have an acceptable benefit-risk profile in such cases because the potential for benefit in the exposed population would generally be small.*"

We recommend that FDA clarify the meaning of "an acceptable benefit-risk profile."

V. B. Risk Assessment and Minimizing the Potential for Medication Errors

Lines 475- 478: " *Sponsors can help minimize the risk of medication errors involving their products by conducting a premarketing risk assessment to document that a product's proprietary name, established name, container label, carton labeling, patient/consumer labeling, professional package insert labeling, and packaging do not inadvertently contribute to medication errors.*"

Aventis suggests that FDA provide a definition of Medication Error in harmony with the ICH definition of programmatic error. It would also be beneficial to include a list of common and frequent medication errors already reported. This could be added to the expanded guidance on medication error prevention analysis that is currently being developed, as quoted in line 512.

VI. A. Describing Adverse Events to Identify Safety Signals

Lines 593-596: "*The severity or magnitude of an event may be inappropriately exaggerated (e.g., if an investigator terms a case of isolated elevated transaminases acute liver failure despite the absence of evidence of associated hyperbilirubinemia, coagulopathy, or encephalopathy, which are components of the standard definition of acute liver failure).*"

We ask the FDA to provide a standard definition of "acute liver failure".

Line 636: "*...constellation of symptoms...*"

We suggest that the meaning of "constellation" in this context be clarified.

<u>Guidance II- Development and Use of Risk Minimization Plans - Docket No. 2004D-0188</u>

<u>General Comments</u>

FDA makes it clear in the proposed guidance that for most products, routine risk minimization measures are sufficient, and that only a few products are expected to have risks warranting a RiskMAP. Furthermore, it should be made clear in the guidance document that patient access to newer products when medically appropriate should not be jeopardized by the existence of a RiskMAP.

The focus of this document is clearly on mechanisms designed to decrease risk. We believe the guidance would be further enhanced if it also addressed interventions designed to increase the

likelihood and/or degree of benefit (e.g., diagnostic tools, prospective identification of high-response subsets). This approach would more completely address the objective of optimizing the benefit risk balance

We suggest that FDA describe how this guidance relates to the suggested submissions described in the ICH E2E draft Guidance on Pharmacovigilance Planning.

Specific Comments

III.A. Relationship Between a Product's Benefits and Risks

Lines 128-130: *"Benefit and risk information emerges continually throughout a product's lifecycle (i.e., during the investigational and marketing phases) and can reflect the results of both labeled and off-label uses."....*
Lines 134-136*"Benefits as well as risks are also patient-specific and are influenced by such factors as the severity of the disease being treated, its outcome if untreated, existing therapeutic options, and the intended patient population."*

We agree that benefit and risk information emerges continually throughout a product's lifecycle and can reflect the results of both labeled and off-label uses. We share the difficulty in assessing the benefits and risks of a drug product, because they are often patient-specific and are influenced by various factors. At present, most benefit-risk assessments are based mainly on a subjective judgment call, and the assessments are often affected by an inordinate emphasis on a very rare or theoretical risk. Any guidance from the agency for an objective benefit risk assessment will be helpful to ensure a consistent thinking process in the drug review process. We suggest that the Agency consider exploring and using models such as Decision Analytic Model in the future to avoid bias in weighing risks in light of benefits.

III. D. Determining When A RiskMAP Should Be Considered

Lines 225-228 : *"For example, opiate drug products have important benefits in alleviating pain but are associated with significant risk of overdose, abuse, and addiction... consider developing RiskMAPs for these products."*

Consider including more examples of what the Agency considers products that may merit consideration for additional risk minimization efforts.

V.A Rationale for RiskMAP Evaluation

Lines 456- 457: *"...RiskMAP evaluation is intended to ensure that the energy and resources expended on risk minimization are actually achieving the desired goals of continued benefits with minimized risks."*
Lines 468-471: *"Generally, FDA anticipates that RiskMAP evaluations would involve the analysis of observational or descriptive data. Statistical hypothesis testing in the context of RiskMAP evaluation would not typically be expected, given the limitations of the data likely to be available. "*

We support that evaluation of the effectiveness of a RiskMAP is important to ensure that the energy and resources expended on risk minimization are actually achieving the desired goals of continued benefits with minimized risks. RiskMAP evaluations would generally involve the analysis of observational or descriptive data . As stated in the guidance, statistical hypothesis testing in the context of RiskMAP evaluation would not typically be expected.

V.B. Considerations in Designing a RiskMAP Evaluation Plan

Lines 482-488: *"The Agency recommends that sponsors select well-defined, evidence-based, and objective performance measures tailored to the particular RiskMAP to determine whether the RiskMAP's goals or objectives are being achieved. An appropriate measure could be a number, percentage, or rate of an outcome, event, process, knowledge, or behavior. Ideally, the chosen measure would directly measure the RiskMAP's health outcome goal. For example, for a RiskMAP with a goal of preventing a particular complication of product use, a sample outcome measure could be to have no more than a specified number or rate of that complication. "*

We agree that ideally the chosen goals would directly measure the RiskMAP's health outcome goals. Sometimes although the outcomes can be measured, it is impossible to define a threshold due to the deficiency of existing data. We suggest that the Agency clarify that simple descriptive data of the outcome measure, without a specified number as a goal, can be presented for RiskMAP evaluations under such circumstances.

V. C. FDA Assessment of RiskMAP Evaluation Results

Line 611-613: *"FDA, in turn, generally would perform its own assessment of RiskMAP effectiveness according to the principles of this guidance."*

We recommend that FDA share the results of its assessment of the RiskMAP effectiveness with the sponsor and discuss any differences of interpretation (reference line 652). Does FDA anticipate including RiskMAP's as a condition of approval of an NDA or BLA or as a postmarketing requirement?

Guidance III- Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment- Docket No. 2004D-0189

General Comments

We feel that certain definitions are not adequately addressed in the draft guidance. For example, the definition of pharmacovigilance is not fully harmonized with the definition of pharmacovigilance contained in the ICH E2E draft guidance on Pharmacovigilance Planning.

We also suggest that FDA include a definition of "signal" in the guidance document, as this term is used frequently throughout the draft document, with apparently different meanings.

Specific Comments

III. THE ROLE OF PHARMACOVIGILANCE IN RISK MANAGEMENT

Line 115- 119: *"In discussing postmarketing risk assessment, this guidance uses the term pharmacovigilance to mean all observational (nonrandomized) post-approval scientific and data gathering activities relating to the detection, assessment, and understanding of adverse events. This includes the use of pharmacoepidemiologic safety studies. These activities are undertaken with the goal of identifying and preventing these events to the extent possible."*

We are concerned that this new definition of pharmacovigilance is not in harmony with the definition of pharmacovigilance contained in the ICH E2E draft guidance, which uses the WHO definition, "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug related problem." A major difference between these two definitions is that the FDA definition is specific to post-approval activities, whereas the ICH/WHO definition does not include this limitation.

IV. IDENTIFYING AND DESCRIBING SAFETY SIGNALS: FROM CASE REPORTS TO CASE SERIES

Definition of "Safety Signal":
Line 121- *"...an excess, compared to what would be expected, of adverse events associated with a product's use."*
Lines 327- 331: *"A signal is operationally defined as any product-event combination with a score exceeding the specified threshold. It is not unusual for a product to have several signals identified using these methods. The lower the threshold, the more likely it is that signals of true effects will be detected, but these lower thresholds will also result in more false positive signals."*
Lines 361-384: *" Safety signals that typically warrant further investigation may include, but are not limited to, the following:*

1. *New unlabeled adverse events, especially if serious;*

2. *An apparent increase in the severity of a labeled event;*
3. *More than a small number of serious events thought to be extremely rare;*
4. *New product-product, product-food, or product-dietary supplement interactions;*
5. *Identification of a previously unrecognized at-risk population (e.g., populations with specific racial or genetic predispositions or co-morbidities);*
6. *Actual or potential confusion about a product's name, labeling, packaging, or use;*
7. *Concerns arising from the way a product is used (e.g., adverse events seen at higher than labeled doses or in populations not recommended for treatment);*
8. *Concerns arising from potential inadequacies of a currently implemented risk minimization action plan (e.g., reports of serious adverse events that appear to reflect failure of a RiskMAP goal); and*
9. *Other concerns identified by the sponsor or FDA."*

We suggest that the Agency include a standard definition of "safety signal"; apparently, this term is used with different meanings throughout the document.

IV.B. Characteristics of a Good Case Report

Line 183-" *7. Information about response to dechallenge and rechallenge"*

We suggest adding "when applicable" (not for vaccines).

Lines188-189: *" For reports of medication errors, good case reports also include full descriptions of the following"*

We suggest that the Agency clarify that these case reports are for adverse events associated with medication errors. We also recommend that the definition of medication errors be included in a glossary, as suggested earlier.

IV.C. Developing a Case Series and Assessing Causality of Individual Case Reports

Lines 217-219: *"FDA recommends that emphasis usually be placed on review of serious, unlabeled adverse events, although other events may warrant further investigation.*

We suggest replacing "unlabeled" by "unexpected." (see also lines 364 and 607)

IV.D Summary Descriptive Analysis of a Case Series

Line 289-307: *" A case series commonly includes an analysis of the following:..... Changes in event reporting rate over calendar time or product life cycle."*

We suggest adding the Lot Number, particularly for vaccines.

IV.E. Use of Data Mining to Identify Product-Event Combinations

Lines 311-317: *" At various stages of risk identification and assessment, looking systematically into the data by using statistical or mathematical tools, or so-called data mining, can provide additional information about the existence or characteristics of a signal. By applying data mining techniques to large adverse event databases, such as FDA's AERS or VAERS, a sponsor may be able to identify unusual or unexpected product-event combinations warranting further investigations. Data mining is not the only technique used to make causal attributions between products and adverse events."*

We support the assertion that data mining may be a useful tool for risk identification in the future, although the full utility of data mining is still under exploration at present. We suggest that the Agency clarify that data mining should not be used to characterize a risk, nor to assess causality. We also suggest that the Agency clarify that the benefits of data mining have not yet been quantified (line 333). Because there is no "gold standard" to which adverse event signals can be compared, therefore it is difficult to establish either a positive or negative predictive value with data mining.

IV.G. Putting the Signal into Context: Calculating Reporting Rates vs. Incidence Rates

Lines 390-396: *"...calculations of the rate at which new cases of adverse events occur in the product-exposed population (i.e., the incidence rate) are the hallmark of pharmacoepidemiologic risk assessment. In pharmacoepidemiologic safety studies (see section V.A), the numerator (number of new cases) and denominator (number of exposed patients and time of exposure) may be readily ascertainable. In contrast, for spontaneously reported events, it is not possible to identify all cases because of under-reporting, and the size of the exposed population is at best an estimate."*

We agree that the calculation of reporting rates can help put signals into context. Incorporating the fact that limitations in denominator estimates depend on the data source and assumptions used to derive these estimates could enhance the document. For instance, the limitations using the IMS sales database are different from those using the National Disease Therapeutic Index (NDTI).

Lines 410-412: *"FDA suggests that sponsors calculate reporting rates by using the total number of spontaneously reported cases in the United States in the numerator and estimates of national patient exposure to product in the denominator."*

We suggest that the Agency clarify that reporting rates should be computed based on not only region-specific data, but also global data. In non-US countries, the sales data is often the only data source available. We suggest that the Agency conform with the same guidance for estimating exposure as outlined in the CIOMS V document, namely: total quantity sold, # of units sold, # of prescriptions or treatments, # of patients, person-time (e.g., treatment-months, person-years), and Defined Daily Dose (DDD).

Lines 425-428: *" To provide further context for incidence rates or reporting rates, it is helpful to have an estimate of the background rate of occurrence for the event being evaluated in the general population or, ideally, in a subpopulation with characteristics similar to that of the exposed population (e.g., premenopausal women, diabetics)."*

We suggest that the Agency emphasize that a direct comparison of a reporting rate of an event with the background incidence rate of the same event should be done with caution, because the reporting rate and incidence rate are computed using different data.

V.A Pharmacoepidemiologic Safety Studies

Lines 469-470: ". Unlike a case series, a pharmacoepidemiologic safety study has a protocol and control group and tests prespecified hypotheses."

We suggest that the Agency clarify that pharmacoepidemiologic studies can be designed not only to test hypotheses, but also to study the natural history of disease or pattern of product use. We also suggest that the Agency clarify that pharmacoepidemiologic studies, such as case-control studies and cohort studies are usually employed to assess the association between drug and outcome, rather than the causality (lines 255-257). Additional data are required to assess causality, and the criteria used for causality assessment include the temporal relationship between exposure and outcome, the strength of the association, dose response, and consistency among studies.

Lines 489-491: *"Because pharmacoepidemiologic safety studies are observational in nature, they are more subject to confounding, effect modification, and other bias, which may make results of these types of studies more difficult to interpret than the results of clinical trials."*

We suggest that the Agency clarify that it is important to be aware of the strengths and limitations of observational studies as well as that of clinical trials. Clinical trials are very costly to conduct, have limited generalizability, and they cannot be employed to assess uncommon or delayed adverse events. Additionally, inappropriate randomization in clinical trials will result in serious bias. Incorporating the methods commonly used to adjust for confounders/effect modifiers and to minimize potential bias in the conduct of observational studies could enhance the document. These methods include random sampling, stratification, matching, and multivariate regression analysis.

V.I. BEYOND ROUTINE PHARMACOVIGILANCE: DEVELOPING A PHARMACOVIGILANCE PLAN

Lines 704-707: *" ... in certain limited instances, unusual safety signals may become evident before approval or after a product is marketed that could suggest that consideration by the sponsor of enhanced pharmacovigilance efforts or a pharmacovigilance plan may be appropriate.*

This document and the ICH E2E draft guidance on Pharmacovigilance Planning both describe a "Pharmacovigilance Plan" (PVP). However, the FDA document indicates that a PVP should be developed if "routine pharmacovigilance" is not sufficient. Specifically, the PVP will only be developed when unusual safety signals have been identified, either before or after approval. This does not seem to be in line with the ICH E2E document, which states: "For products for which no special concerns have arisen, routine pharmacovigilance activities might be considered adequate for the Pharmacovigilance Plan".

We strongly urge the FDA to incorporate the terminology and definitions used in the final ICH E2E guidance document.

On behalf of Aventis Inc. and Aventis Pasteur we appreciate the opportunity to comment on the draft guidances for industry entitled *"Premarketing Risk Assessment", "Development and Use of Risk Minimization Action Plans", and "Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment".*

Sincerely,

Steve Caffé, M.D.
Vice President, Head U.S. Regulatory Affairs

On behalf of:

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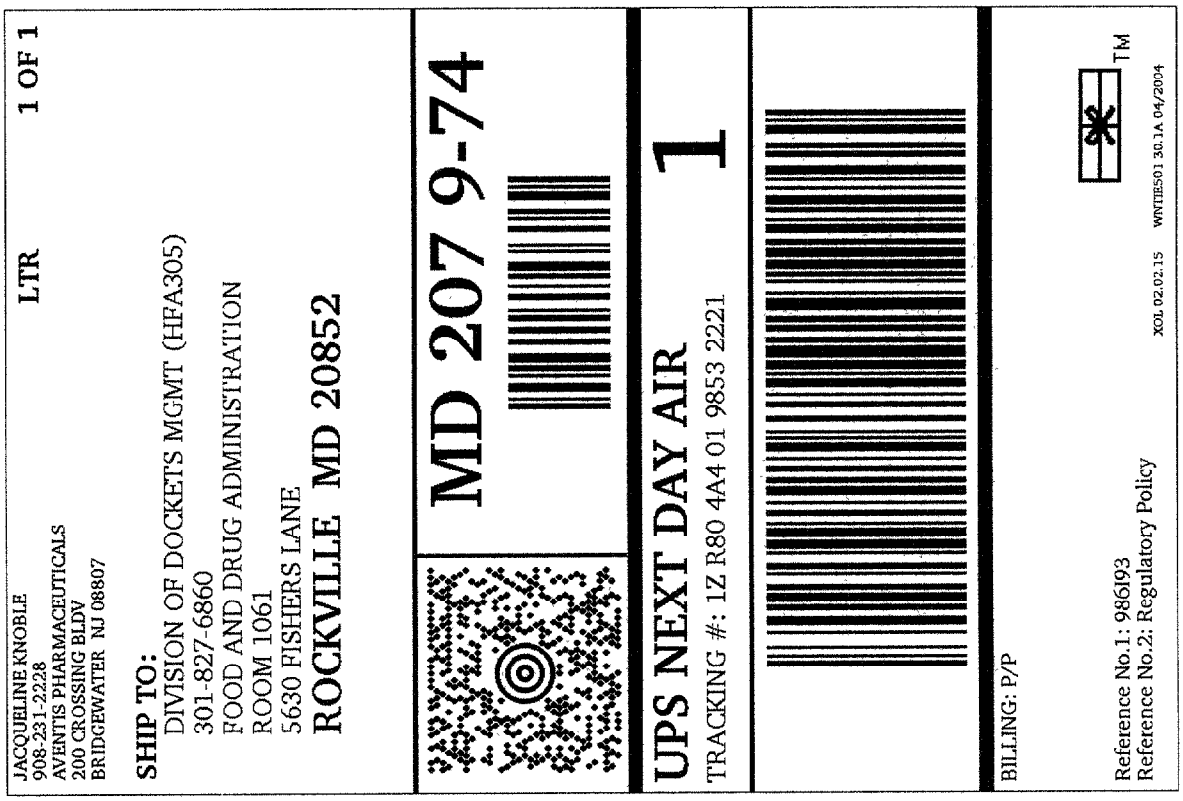

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